REMARKS

I. Introduction

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

Claims 1-37, 54, and 61-63 are requested to be cancelled. The cancellation of claims does not constitute acquiescence in the propriety of any rejection set forth by the Examiner. Applicants reserve the right to pursue the subject matter of the canceled claims in subsequent divisional applications.

Claims 57-60 and 64 are currently being amended.

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claims remain under examination in the application, is presented, with an appropriate defined status identifier.

Upon entry of this Amendment, claims 38-53, 55-60, and 64-66 will remain pending in the application.

Because the foregoing amendments do not introduce new matter, entry thereof by the Examiner is respectfully requested.

II. Response to Issues Raised by Examiner in Outstanding Office Action

a. Claim Rejections - 35 U.S.C. § 112, First Paragraph

Claims 58 and 64-66 are rejected by the Examiner under 35 U.S.C. § 112, first paragraph for lack of enablement. Applicants respectfully request reconsideration and withdrawal of the rejection.

The Examiner asserts that the specification does not reasonably provide enablement for inducing immune responses and vaccines against all unstable proteins. In addition the

examiner states that the specification does not enable any person skilled in the art to use the invention commensurate with these claims.

The methods described in the specification and claimed by the Applicants have enabled a wide range of successful studies regarding vaccines and immune responses. For example, vaccination with plasmid DNA encoding Hsp-binding T-Ag variants or T-fusion proteins elicits humoral immune responses. Using a process taught in the specification by Examples 1-4, pages 24-30, fusion proteins carrying an N-terminal T77 domain were efficiently expressed in transfected cells. Vaccination studies showed that enhanced expression correlated with an efficient induction of antibody responses against the fusion protein *in vivo*. This was demonstrated using a Hepatitis B virus core domain (C79-149) fused to the T77 fragments. This study was described in: R. Schirmbeck R., M. Kwissa, N. Fissolo, S. ElKholy, P. Riedl and J. Reimann. "Priming polyvalent immunity by DNA vaccines expressing chimeric antigens with a stress protein- capturing, viral J-domain." (2002) *FASEB J.* 16: 1108, and provided with the 12/29/2003 Response to Office Action.

Thus, expression of the hsp73-capturing T77/C79-149 fusion protein enhanced the immunogenicity of the C79-149 domain for B cells. These findings extend the data described in example 8, where Applicants show that hsp-binding SV40 T-Ag variants (but not the non-hsp bound wild type T-Ag) induce T-Ag specific serum antibodies, which further indicates that the data described in Example 9 of the present specification (for the generation of anti preS1/S2 antibodies) can be reproduced in other antigen systems.

In further support that the present invention is adequately enabled, applicants also provided a review article with the Response to Office Action dated 12/29/2003 authored by the inventors and published in the journal, *Immunological Reviews*, (see Attachment E of 12/29/2003 Office Action). The article supports that the claimed polynucleotides, vectors, host cells and methods are supported over the whole claimed range of the invention. Particularly, Table III of this review shows that the antigens expressed as hsp capturing, chimeric antigens have a half life of more than 12 hours. Also submitted for the Examiner was a list of constructs 1–47 provided by the inventors, showing the successful production in the "hsp-facilitated expression system" (See Attachment B and Table 1 from Attachment F of

12/29/2003 Response to Office Action). These data provide additional evidence of the adequate and wide ranging enablement of the present specification. In particular, Applicants point out the success for SIV constructs using the methodology described (See Figure 1 of specification and see Attachment B and Table 1 from Attachment F of 12/29/2003 Response to Office Action).

The present inventors have provided an inexpensive and efficient means that reliably allows the expression of (poly)peptides within cells via the Hsp73/T-Ag system and successfully presents these polypeptides to the immune system. Applicants submit that this contribution to the field entitles the inventors to claim their invention in a manner which provides adequate coverage for their contribution, and applicants maintain that the disclosure supports this general principle and provides enablement to one of ordinary skill in the art. It is not mandatory, and is practically impossible, to disclose in the description, each and every potential embodiment which might be derived from a generic claim. Applicants submit that the above information, the supporting documents from the 12/23/2003 Response to Office Action, and the disclosure in the specification as outlined above, provide sufficient evidence that the specification provides adequate enablement and support for success using a wide range of proteins and immunological environments. . In view of these arguments and documents, it is requested that this rejection be withdrawn.

b. Claim Rejections - 35 U.S.C. § 103

Claims 38-53, 55, 56, 59, 60, and 64-66 are rejected by the Examiner under 35 U.S.C. § 103 as being obvious over Schimbeck *et al.* and Fu *et al.*. Applicants respectfully request reconsideration and withdrawal of the rejection.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the

reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). See, also MPEP §2143.01. In the pending case, the examiner has failed to establish a *prima facie* case of obviousness.

Schimbeck *et al* describes the expression of hsp capturing, mutant T-antigen in mutant cell lines, and TAP independent, MHC class 1- restricted presentation of some (but not all) epitopes of the T antigen by these cells. This study does not address the use of the expression system as a DNA vaccine to deliver antigen in immunogenic form. In fact, TAP-deficient individuals would not even benefit from a vaccine because they have no $CDC8^+$ T cells. Many key elements necessary for a vaccine are not deducible from these studies.

Fu, *et al* describes how known antigenic epitopes of unrelated antigens can be spliced in frame into the sequence of the SV40 T-antigen. Cells are transfected with these constructs in order to 1) immortalize them and 2) present the respective epitopes in the context of MHC class 1 molecules. This study establishes a T cell readout system that supports non-quantitative detection of specific T cell reactivities. There is no connection to vaccination, immunogenic presentation *in vivo*, hsp association, and other aspects of the claimed invention.

The examiner has used impermissible hindsight to try and combine these two studies in order to create an obviousness rejection. Due to the limitations given with regard to the cited references, the examiner is requested to withdraw his §103 obviousness rejection.

CONCLUSION

The present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant(s) hereby petition(s) for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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By _____

FOLEY & LARDNER LLP
Customer Number:
22428
PATENT TRADEMARK OFFICE
Telephone: (202) 672 5483
Facsimile: (202) 672-5399

Richard Peet
Attorney for Applicant
Registration No. 35,792